

Original Contribution

Recent Exposure to Particulate Matter and C-reactive Protein Concentration in the Multi-Ethnic Study of Atherosclerosis

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Ambient levels of particulate matter have been linked to cardiovascular disease. The mechanisms mediating these associations are poorly understood. One candidate mechanism is inflammation. Using data from the Multi-Ethnic Study of Atherosclerosis (2000–2002), the authors investigated the relation between exposure to particulate matter of less than or equal to 2.5 μm in diameter ($\text{PM}_{2.5}$) and C-reactive protein concentration in 5,634 persons aged 45–84 years who were free of cardiovascular disease. Data from US Environmental Protection Agency monitors were used to estimate $\text{PM}_{2.5}$ exposures for the prior day, prior 2 days, prior week, prior 30 days, and prior 60 days. Only the 30-day and 60-day mean exposures showed a weak positive association with C-reactive protein, and confidence intervals were wide: relative increases in C-reactive protein per 10 $\mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ adjusted for person-level covariates were 3% (95% confidence interval (CI): –2, 10) for a 30-day mean and 4% (95% CI: –3, 11.0) for a 60-day mean. The means of 7-day, 30-day, and 60-day exposures were weakly, positively, and nonsignificantly associated with the odds of C-reactive protein of greater than or equal to 3 mg/liter: adjusted odds ratios were 1.05 (95% CI: 0.96, 1.15), 1.12 (95% CI: 0.98, 1.29), and 1.12 (95% CI: 0.96, 1.32), respectively. Slightly stronger associations were observed in persons without other risk factors for elevated C-reactive protein, but this heterogeneity was not statistically significant. The authors' results are not compatible with strong effects of particulate matter exposures on population levels of C-reactive protein.

air pollutants, environmental; cardiovascular diseases; inflammation

Abbreviations: CI, confidence interval; MESA, Multi-Ethnic Study of Atherosclerosis; $\text{PM}_{2.5}$, particulate matter of less than or equal to 2.5 μm in diameter; PM_{10} , particulate matter of less than or equal to 10 μm in diameter.

A growing body of work has linked ambient levels of particulate matter to cardiovascular disease morbidity and mortality (1–6), but the mechanisms mediating these asso-

ciations are still poorly understood. One of several plausible biologic mechanisms linking particulate matter exposure to cardiovascular risk is increased inflammation (7–9). It has

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been postulated that the interaction of alveolar macrophages with atmospheric particles results in increased oxidant production and the release of inflammatory mediators (10), which may in turn participate in the development of atherosclerotic disease or the precipitation of clinical events in persons with underlying disease (11). Ultrafine particles may also exert systemic effects through direct passage of particles into the blood circulation (12).

Experimental evidence from animal and human studies has shown that exposure to inhaled particles is associated with local inflammatory changes in the lung and may result in a systemic inflammatory response (13–18). However, there is still limited evidence on the extent to which exposure to particulate matter is associated with changes in levels of systemic inflammatory markers in the general population. Although two epidemiologic studies have reported positive associations between recent exposures to particles and markers of the acute phase response such as C-reactive protein and fibrinogen (19, 20), other studies have reported associations limited to the summer months (21), associations present for ambient exposures but not personal exposure (22), positive associations that disappear when highly influential observations are excluded (23), and even negative associations (22).

Most prior studies of exposure to particles and inflammatory markers have investigated relatively short lags, ranging from exposures the same day to exposures during the 5 prior days. However, it is plausible that repeated exposures have effects that accumulate over time. The presence of cumulative effects is consistent with recent work showing that exposures occurring more remotely (in some cases during the prior 1–2 months) are associated with all-cause and cardiovascular mortality in time series analyses (24–26), although results regarding the effects of recent and long-term exposures on cardiovascular mortality have not always been consistent (27). No studies have investigated long-term exposures in relation to C-reactive protein levels in population-based samples.

Using data from a large, multiethnic, population-based study of atherosclerosis, we investigated the relation between recent exposure to particulate matter of less than or equal to 2.5 μm in diameter ($\text{PM}_{2.5}$) and levels of inflammatory markers. We hypothesized that recent exposure to $\text{PM}_{2.5}$ would be positively associated with higher C-reactive protein concentration, after adjustment for potential confounders. We also investigated lags ranging from the prior day to the prior 2 months. The confirmation of a relation between air particulate exposure and markers of systemic inflammation would lend support for a mechanistic pathway linking air pollution to cardiovascular disease, and it would also suggest that exposure to particulate matter may be etiologically relevant to other diseases processes in which inflammation may play a causal role.

MATERIALS AND METHODS

Subjects

The Multi-Ethnic Study of Atherosclerosis (MESA) (28) is a longitudinal study supported by the National Heart,

Lung, and Blood Institute with the overall goal of identifying risk factors for subclinical atherosclerosis. A total of 6,814 men and women, who identified themselves as White, Black, Hispanic, or Chinese and were aged 45–84 years and free of clinically apparent cardiovascular disease, were recruited from portions of six US communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. Each site recruited by randomly selecting potential participants from locally available sources (lists of residents or dwellings) or using random digit dialing. Details of the sampling plan have been previously reported (28). Among those screened and deemed eligible, the participation rate was 59.8 percent. The baseline visit for the cohort (on which these analyses are based) took place between June 2000 and August 2002.

Measurements and variable definitions

Pollutant data were extracted from the US Environmental Protection Agency's Aerometric Information Retrieval System (AIRS) in November 2003 (29). $\text{PM}_{2.5}$ concentrations were obtained from 24-hour samples, some of which collected data daily, but most of which collected data every third day. For each person, we constructed a set of cumulative exposure measures for the 60 days prior to the day on which blood was drawn. Each daily exposure was based on the monitor nearest to the person's residence with available data on that day. This ensured that complete data were available for most participants but, because most monitors collected data every third day, the monitor from which data were drawn could differ for different days. The mean distance to the nearest monitor was 9 km (distance ranged from 0.45 to 51 km). Five exposure measures were constructed by use of the 60-day lags: prior day, average of prior 2 days, average of prior week, average of prior month, and average of prior 2 months.

C-reactive protein was measured in all participants at baseline using a Behring nephelometer II (BNII) automated immunoanalyzer (N High Sensitivity CRP assay; Dade Behring, Inc., Deerfield, Illinois) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). Site and central laboratory quality control procedures are reported elsewhere (28). Intraassay coefficients of variation range from 2.3 to 4.4 percent, and interassay coefficients of variation range from 2.1 to 5.7 percent. C-reactive protein values were highly skewed and were log transformed for analyses. Individual-level variables known to be associated with C-reactive protein concentrations that could also covary with day of visit (and hence with particulate matter levels) were examined as covariates (refer to table 1 for list). Because $\text{PM}_{2.5}$ concentrations vary by site and site could be associated with C-reactive protein concentrations through other mechanisms, results are also shown after additional adjustment for site. Selected analyses were also repeated for interleukin-6, another inflammatory marker. Interleukin-6 was measured by an ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS human interleukin-6 immunoassay; R&D Systems, Minneapolis, Minnesota).

TABLE 1. Demographic characteristics, exposure to particulate matter of ≤ 2.5 μm in diameter, and C-reactive protein concentrations for the 5,634 participants included in the analyses, Multi-Ethnic Study of Atherosclerosis, 2000–2002

Age, years (mean (SD*))	61.99 (10.13)
% female	52.6
Race/ethnicity (% distribution)	
Caucasian	40.3
Chinese	12.1
African American	26.5
Hispanic	21.1
Study site (% distribution)	
Baltimore, MD	15.7
Chicago, IL	18.1
Forsyth County, NC	15.7
Los Angeles, CA	19.0
New York City, NY	16.0
St. Paul, MN	15.5
Self-reported health (% distribution)	
Poor	0.6
Fair	7.8
Good	40.7
Very good	34.3
Excellent	16.7
Body mass index, kg/m^2 (mean (SD))	28.25 (5.37)
Diabetes (% distribution)†	
No	58.5
Impaired glucose tolerance	28.1
Diabetes	13.5
Smoking status (% distribution)	
Never	50.8
Former	36.8
Current	12.3
Secondhand smoke (% distribution)‡	
None	53.0
At least 1 hour per week	34.7
Current smokers	12.3

Table continues

Other gaseous pollutants (sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone) and weather variables (temperature and dew point temperature) were included as covariates in some models because of their association with $\text{PM}_{2.5}$ and their potential effects on C-reactive protein concentrations. Nitrogen dioxide and sulfur dioxide daily averages were computed by averaging hourly data if at least 20 hours of data were recorded for a 24-hour period. Ozone and carbon monoxide were represented by the maximum 8-hour running average for a 24-hour period. Measures of daily average temperature, dew point temperature, and sea level barometric pressure were obtained from a National Weather Service monitoring station that was representative of each study area.

TABLE 1. Continued

Physical activity (% distribution)§	
Low	25.1
Medium	47.3
High	27.6
% with arthritis flare within past 2 weeks¶	12.2
% with regular use of any nonsteroidal antiinflammatory drugs, aspirin, or lipid-lowering medications¶	45.4
% with infections within past 2 weeks¶	23.2
$\text{PM}_{2.5}$,* $\mu\text{g}/\text{m}^3$ (median (25th, 75th percentiles))	
Prior day	14.30 (9.50, 20.90)
Prior 2 days#	14.40 (10.15, 20.35)
Prior 7 days#	15.24 (12.07, 19.70)
Prior 30 days#	15.69 (13.07, 19.22)
Prior 60 days#	15.90 (13.77, 19.08)
C-reactive protein, mg/liter (median (25th, 75th percentiles))	1.84 (0.82, 4.10)

* SD, standard deviation; $\text{PM}_{2.5}$, particulate matter of less than or equal to 2.5 μm in diameter.

† American Diabetes Association 2003 criteria: "impaired" is fasting glucose of 100–125 mg/dl ; "diabetic" is fasting glucose of ≥ 126 mg/dl or takes insulin or oral diabetes medication.

‡ Asked of only noncurrent smokers. Noncurrent smokers missing secondhand smoke information ($n = 144$) were assigned to no secondhand smoke.

§ Physical activity was based on total minutes per day and categorized into three levels with the lowest level being the lowest quartile, the middle level being the 25th–75th percentiles, and the highest level being the highest quartile.

¶ Persons missing arthritis, medication, or infection information ($n = 5$, $n = 21$, or $n = 6$, respectively) were assigned to no arthritis, no medication, or no infection, respectively. "Infection" was defined as cold, flu, bronchitis, sinus infection, tooth infection, or urinary tract infection.

Sample sizes for exposures were smaller than for the full sample because of missing data; $n = 5,606$, 5,510, 5,294, and 5,136 for the prior 2 days, prior 7 days, prior 30 days, and prior 60 days, respectively.

Cumulative exposures for copollutants and weather replicated the lagged averaging scheme described for $\text{PM}_{2.5}$.

Data analysis

Scatterplots, LOESS smoothing by SAS/STAT software (SAS Institute, Inc., Cary, North Carolina), and generalized additive models (30) were initially used to investigate the shape of the relation between each of our five measures of exposure and log C-reactive protein concentration. Linear regression was then used to estimate the associations of $\text{PM}_{2.5}$ exposures with C-reactive protein concentration before and after adjustment for the individual-level covariates, study site, copollutants, and weather. The presence of seasonal trends was investigated by examining seasonal patterns in the residuals of fully adjusted models. We tested for the presence of residual autocorrelation using the Durbin-Watson d statistic.

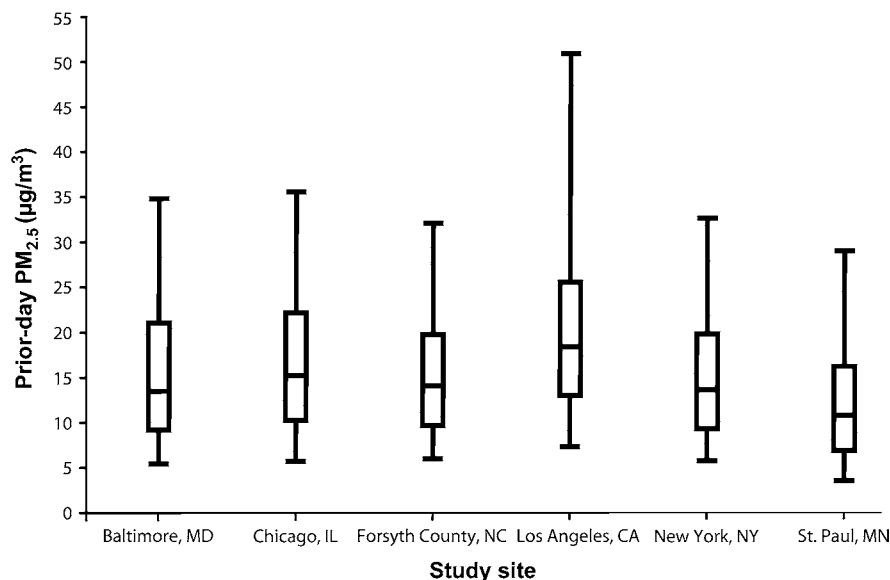


FIGURE 1. Distribution of particulate matter of ≤ 2.5 μm in diameter ($\text{PM}_{2.5}$) by study site, Multi-Ethnic Study of Atherosclerosis, 2000–2002. Boxes represent the 25th percentile, median, and 75th percentile; box plot whiskers represent the 5th–95th percentiles.

Stratified analyses were conducted to investigate if effects differed across site, season (warmer months vs. cooler months), or individual-level variables (age, sex, race/ethnicity, education, self-reported health, diabetes, infection, medication use, and history of asthma, bronchitis, or emphysema). Additive interactions in the log scale (or effect measure modification for relative differences) were tested by including interaction terms in regression models. In order to examine if $\text{PM}_{2.5}$ exposure was related to C-reactive protein only among persons without other factors strongly related to inflammation, we also repeated the analyses, excluding persons with any of the following characteristics/conditions: self-reported fair/poor health, impaired glucose tolerance or diabetes, current cigarette smoking, recent arthritis flare, taking antiinflammatory or lipid-lowering medications, or recent infection.

We examined the sensitivity of results to alternate ways of estimating exposure by 1) restricting analyses to participants with monitors within 9 km of their home (9 km being the mean distance in our sample) and 2) using the average of all available monitors within the city of residence (defined as 40 km or 25 miles from the centroid of participant residences) as the exposure measure instead of the nearest monitor. In additional sensitivity analyses for a subset of the data, we compared results using the nearest monitor with results obtained by estimating exposure at each residence using inverse distance interpolation and space-time kriging with a separable covariance model (31, 32). These sensitivity analyses were conducted for the site with the greatest within-site variability in exposure (Los Angeles). In secondary analyses, selected (logistic) models were also run using C-reactive protein of greater than or equal to 3 mg/liter (the cutoff used to define high-risk groups on the basis of C-reactive protein concentration) (33) as a binary outcome.

Of the 6,814 participants who completed the baseline examination, 6,069 participated in the air pollution study. Of these, 147 were excluded because latitude and longitude coordinates for their address were unavailable, 26 participants were excluded because of missing data on prior day $\text{PM}_{2.5}$ exposure, and 262 participants were excluded because of missing data on C-reactive protein or key covariates of interest, yielding a total of 5,634 participants (83 percent of the total cohort) for analysis. Analyses of long-term exposures excluded additional participants because of missing exposure data.

RESULTS

The mean participant was 62 years of age, and 53 percent were female. Additional characteristics of the study sample are shown in table 1. The median $\text{PM}_{2.5}$ for the set of cumulative exposures investigated ranged from 14.3 $\mu\text{g}/\text{m}^3$ for prior day to 15.9 $\mu\text{g}/\text{m}^3$ for prior 60 days. The median C-reactive protein level was 1.84 mg/liter. Approximately 35 percent of participants had C-reactive protein concentrations of greater than or equal to 3 mg/liter. Median prior day $\text{PM}_{2.5}$ exposure levels were lowest in St. Paul (10.6 $\mu\text{g}/\text{m}^3$) and highest in Los Angeles (18.3 $\mu\text{g}/\text{m}^3$) (figure 1). A similar pattern was observed for the mean of the prior 60 days (not shown). Correlations between prior day exposure and other exposures were 0.91, 0.60, 0.43, and 0.36 for prior 2 days, prior 7 days, prior 30 days, and prior 60 days, respectively (all $p < 0.001$). Other pairwise correlations between exposures lay between this range. Virtually all (99 percent) participants were within 40 km of the centroid for the site. Of the total variance in $\text{PM}_{2.5}$ measures, the majority (74–87 percent depending on the site) were

between days (within season), and only a small proportion (7–19 percent) were between monitors within days.

C-reactive protein concentrations were positively associated with age, female gender, Hispanic ethnicity, body mass index, diabetes, current smoking status, secondhand smoke, infections, and living in Forsyth County (table 2). Self-reported health, physical activity, and arthritis flare were also associated with C-reactive protein in the expected direction, although differences were not statistically significant. In unadjusted bivariate analyses, there was no evidence of an association between $PM_{2.5}$ levels and C-reactive protein concentration. Analyses using generalized additive models (with adjustment for person-level covariates) also revealed no evidence of a clear threshold for the effect of $PM_{2.5}$ on C-reactive protein for any of the exposures studied for the range of $PM_{2.5}$ levels within which the majority of study participants were found (data available from authors upon request).

Table 3 shows relative differences in C-reactive protein per $10\text{-}\mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ for the range of models fitted. Overall, there was no clear evidence of a positive association between $PM_{2.5}$ exposure and C-reactive protein concentration for any of the exposures studied. $PM_{2.5}$ levels for the prior day, prior 2 days, and prior 7 days were not positively associated with C-reactive protein. In models adjusted for person-level covariates, only the 30-day and 60-day exposures (in some models) showed a positive association with C-reactive protein, but differences were small and all confidence intervals included the null value. Compared with models adjusted for only person-level covariates, site, copollutant, and weather adjustment resulted in associations that were slightly more negative (for prior day, prior 2 days, and prior week) or closer to the null (for prior 30 and 60 days) (table 3). Sensitivity analyses using the study site average as the exposure and restricting the sample to persons within 9 km of a monitor (the mean distance to a monitor in our sample) (table 3) revealed generally similar results. In Los Angeles (the site with the greatest within-site variability in $PM_{2.5}$), results obtained using inverse distance interpolation and space-time kriging were very similar to those obtained using the nearest monitor for all lags studied (not shown). Plots of residuals from adjusted models against time/season showed no clear evidence of seasonal or time trends. Durbin-Watson d statistics did not indicate the presence of first-order autocorrelation. No consistent associations between particulate matter exposure and C-reactive protein concentrations were observed when selected models for continuous C-reactive protein were repeated for exposures to particulate matter of less than or equal to $10\text{ }\mu\text{m}$ in diameter (PM_{10}) (not shown).

Figure 2 shows the relative difference in C-reactive protein per $10\text{-}\mu\text{g}/\text{m}^3$ difference in prior day $PM_{2.5}$ for the restricted sample (participants without other risk factors for elevated C-reactive protein) compared with that of all other participants. Although point estimates suggested weakly positive associations with C-reactive protein in the restricted sample for 30- and 60-day mean exposures, tests for interaction were not statistically significant. Of all the other interactions tested ($PM_{2.5}$ with age, sex, education, diabetes, smoking, use of medications, history of infection, or history

TABLE 2. Adjusted* relative difference in C-reactive protein (mg/liter) for the 5,634 participants included in the analyses, Multi-Ethnic Study of Atherosclerosis, 2000–2002

	Relative difference	95% confidence interval
Age (per 10 years)	1.09	1.05, 1.12
Gender		
Female vs. male	1.54	1.46, 1.63
Race		
Caucasian	Referent	
Chinese	0.72	0.64, 0.8
African American	1.04	0.97, 1.12
Hispanic	1.14	1.04, 1.24
Study site		
Chicago, IL	Referent	
Baltimore, MD	1.01	0.92, 1.11
Forsyth County, NC	1.19	1.08, 1.30
Los Angeles, CA	1.09	0.99, 1.21
New York City, NY	0.91	0.82, 1.00
St. Paul, MN	1.05	0.95, 1.16
Self-reported health		
Poor	1.41	0.98, 2.02
Fair	1.13	1.00, 1.27
Good	1.08	0.99, 1.17
Very good	1.04	0.96, 1.13
Excellent	Referent	
Body mass index (per kg/m^2)	1.08	1.07, 1.09
Diabetes		
No	Referent	
Impaired glucose tolerance	1.09	1.02, 1.16
Diabetic	1.05	0.97, 1.15
Smoking status		
Never	Referent	
Former	1.05	0.99, 1.11
Current	1.42	1.30, 1.55
Secondhand smoke		
None	Referent	
Any	1.09	1.03, 1.15
Physical activity		
Low	Referent	
Medium	0.94	0.88, 1.01
High	0.93	0.86, 1.01
Arthritis		
Flare vs. no flare	1.05	0.96, 1.14
Medications†		
Use vs. no use	0.91	0.86, 0.96
Infections in past 2 weeks†		
Yes vs. no	1.21	1.13, 1.28

* Each estimate is adjusted for all the other variables in the table. The relative difference indicates the percent increase in mean C-reactive protein associated with the variable in question. For example, a relative difference of 1.5 indicates that C-reactive protein is 50% higher in the exposed than in the unexposed group.

† Persons missing medication or infection information ($n = 21$ or $n = 6$, respectively) were assigned to no medication or no infection, respectively. "Infection" was defined as cold, flu, bronchitis, sinus infection, tooth infection, or urinary tract infection.

TABLE 3. Adjusted relative difference in C-reactive protein (mg/liter) per 10- $\mu\text{g}/\text{m}^3$ increase in particulate matter of $\leq 2.5 \mu\text{m}$ in diameter, Multi-Ethnic Study of Atherosclerosis, 2000–2002

Exposure data and adjustment variables	Source of exposure data	No.*	Relative difference	95% confidence interval
Prior day				
Age, gender, race†	Nearest monitor	5,634	0.98	0.96, 1.01
All person-level covariates‡	Nearest monitor	5,634	0.99	0.96, 1.01
All person-level covariates and site§	Nearest monitor	5,634	0.98	0.96, 1.01
All person-level covariates, site, copollutants, and weather¶	Nearest monitor	5,047#	0.97	0.94, 1.01
All person-level covariates and site§	Study site average**	5,572#	0.98	0.96, 1.01
All person-level covariates and site§	Nearest, limited to 9 km	2,831#	0.96	0.92, 1.00
Prior 2 days				
Age, gender, race†	Nearest monitor	5,606	0.97	0.94, 1.00
All person-level covariates‡	Nearest monitor	5,606	0.99	0.96, 1.01
All person-level covariates and site§	Nearest monitor	5,606	0.98	0.95, 1.01
All person-level covariates, site, copollutants, and weather¶	Nearest monitor	5,023#	0.97	0.93, 1.01
All person-level covariates and site§	Study site average**	5,498#	0.98	0.95, 1.01
All person-level covariates and site§	Nearest, limited to 9 km	2,803#	0.96	0.91, 1.00
Prior 7 days				
Age, gender, race†	Nearest monitor	5,510	0.98	0.94, 1.02
All person-level covariates‡	Nearest monitor	5,510	1.00	0.96, 1.04
All person-level covariates and site§	Nearest monitor	5,510	0.99	0.95, 1.04
All person-level covariates, site, copollutants, and weather¶	Nearest monitor	4,913#	0.99	0.93, 1.04
All person-level covariates and site§	Study site average**	5,187#	1.00	0.95, 1.04
All person-level covariates and site§	Nearest, limited to 9 km	2,237#	0.98	0.91, 1.06
Prior 30 days				
Age, gender, race†	Nearest monitor	5,294	0.99	0.93, 1.06
All person-level covariates‡	Nearest monitor	5,294	1.03	0.98, 1.10
All person-level covariates and site§	Nearest monitor	5,294	1.02	0.95, 1.10
All person-level covariates, site, copollutants, and weather¶	Nearest monitor	4,579#	1.02	0.94, 1.12
All person-level covariates and site§	Study site average**	4,307#	1.03	0.96, 1.12
All person-level covariates and site§	Nearest, limited to 9 km	925#	1.09	0.89, 1.34
Prior 60 days				
Age, gender, race†	Nearest monitor	5,136	0.98	0.91, 1.05
All person-level covariates‡	Nearest monitor	5,136	1.04	0.97, 1.11
All person-level covariates and site§	Nearest monitor	5,136	1.02	0.93, 1.11
All person-level covariates, site, copollutants, and weather¶	Nearest monitor	4,219#	0.99	0.89, 1.11
All person-level covariates and site§	Study site average**	3,813#	1.01	0.91, 1.13
All person-level covariates and site§	Nearest, limited to 9 km	369#	0.90	0.47, 1.73

* For each exposure, all persons with complete data were included. Sample size varies by exposure measure because of missing data.

† Model variables: age (1 df), gender (1 df), and race/ethnicity (3 df).

‡ Model variables: age (1 df), gender (1 df), race/ethnicity (3 df), general health status (4 df), body mass index (1 df), diabetes (2 df), cigarette status (2 df), secondhand smoke (1 df), physical activity (2 df), arthritis flare in last 2 weeks (1 df), medications (aspirin, lipids, nonsteroidal antiinflammatory drugs) (1 df), and infections in last 2 weeks (1 df).

§ Model variables: age (1 df), gender (1 df), race/ethnicity (3 df), general health status (4 df), body mass index (1 df), diabetes (2 df), cigarette status (2 df), secondhand smoke (1 df), physical activity (2 df), arthritis flare in last 2 weeks (1 df), medications (aspirin, lipids, nonsteroidal antiinflammatory drugs) (1 df), infections in last 2 weeks (1 df), and study site (5 df).

¶ Model variables: age (1 df), gender (1 df), race/ethnicity (3 df), general health status (4 df), body mass index (1 df), diabetes (2 df), cigarette status (2 df), secondhand smoke (1 df), physical activity (2 df), arthritis flare in last 2 weeks (1 df), medications (aspirin, lipids, nonsteroidal antiinflammatory drugs) (1 df), infections in last 2 weeks (1 df), study site (5 df), sulfur dioxide (1 df), nitrogen dioxide (1 df), carbon monoxide (1 df), ozone (1 df), average temperature (1 df), and dew point temperature (1 df).

Addition of copollutants/weather or study site average or nearest monitor within 9 km resulted in a smaller number of observations because of missing data.

** Based on the average of all monitors within 40 km of the study site centroid.

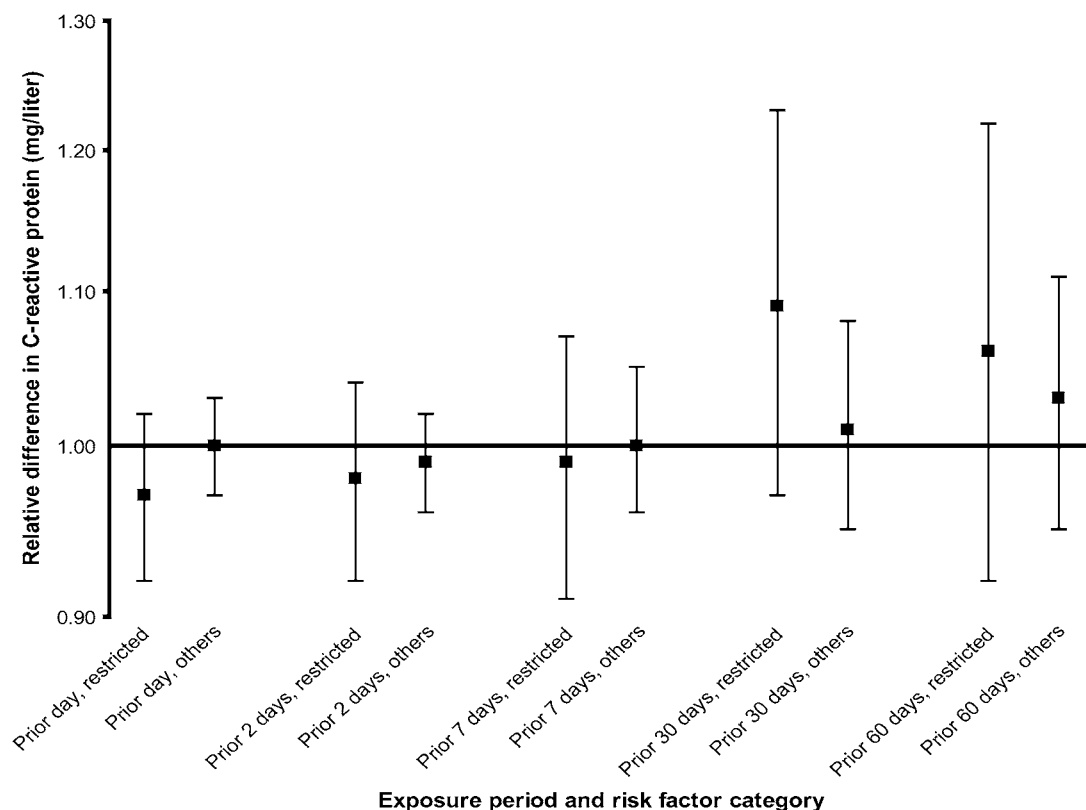


FIGURE 2. Relative differences (with 95% confidence intervals) in C-reactive protein (mg/liter) per $10\text{-}\mu\text{g}/\text{m}^3$ increase in particulate matter of $\leq 2.5\text{ }\mu\text{m}$ in diameter for different exposure periods in a restricted sample without risk factors for elevated C-reactive protein and in the rest of the sample, adjusted for person-level covariates, Multi-Ethnic Study of Atherosclerosis, 2000–2002. The “restricted” sample (20%, $n = 1,123$) are non-smokers without a history of recent infection or arthritis, in good to excellent health, with normal glucose, and who are not taking antiinflammatory medications; “others” are the participants not in the restricted sample. Analyses were adjusted for age, gender, race/ethnicity, general health status, body mass index, diabetes, cigarette smoking, secondhand smoke, physical activity, arthritis flare, medications, and infections. The p values for interaction between exposure and sample group (restricted vs. other) were 0.4, 0.7, 0.8, 0.4, and 0.8 for the prior day, prior 2 days, prior 7 days, prior 30 days, and prior 60 days, respectively.

of lung disease), only season revealed statistically significant interactions consistently across lags. Associations were generally negative for the warm season (March–August) and null or weakly positive for the cool season (September–February) (relative difference per $10\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$: 0.95 (95 percent confidence interval (CI): 0.92, 0.99) and 1.01 (95 percent CI: 0.97, 1.05) for prior day exposure in warm and cool seasons, respectively, and 0.92 (95 percent CI: 0.80, 1.05) and 1.06 (95 percent CI: 0.93, 1.21) for 60-day exposure in warm and cool seasons, respectively).

In analyses with C-reactive protein of greater than or equal to 3 mg/liter as a dichotomous outcome, weak positive associations between $\text{PM}_{2.5}$ exposures and C-reactive protein were observed for some of the models for prior 7-, 30-, and 60-day means, but confidence intervals were wide and included the null value (table 4). In most cases, adjustment for site, copollutants, and weather resulted in estimates even closer to the null. Associations of $\text{PM}_{2.5}$ exposures with the odds of C-reactive protein of greater than or equal to 3 mg/liter appeared to be stronger or present only in participants without other risk factors for elevated C-reactive protein, but

tests for interaction did not achieve statistical significance (figure 3). No positive associations between particulate matter exposures were observed when selected analyses were repeated using interleukin-6 as the outcome.

DISCUSSION

We found no consistent evidence that recent exposure to $\text{PM}_{2.5}$ levels is positively associated with C-reactive protein concentration in a population-based sample. Of the five exposure measures investigated (prior day, prior 2 days, prior week, prior 30 days, and prior 60 days), only the 30-day and 60-day mean exposures showed the expected positive association in analyses of log C-reactive protein as a continuous outcome (3–4 percent increase per $10\text{-}\mu\text{g}/\text{m}^3$ difference in $\text{PM}_{2.5}$ in models adjusted for person-level covariates). The mean 7-, 30-, and 60-day exposures were weakly, positively, and nonsignificantly associated with the odds of C-reactive protein of greater than or equal to 3 mg/liter after adjustment for person-level covariates (increased odds ranging from 5 percent to 12 percent depending on the model).

TABLE 4. Odds ratios of C-reactive protein of ≥ 3 mg/liter per $10\text{-}\mu\text{g}/\text{m}^3$ increase in particulate matter of $\leq 2.5\text{ }\mu\text{m}$ in diameter, Multi-Ethnic Study of Atherosclerosis, 2000–2002

Exposure data and adjustment variables	No.	Odds ratio	95% confidence interval
Prior day			
Age, gender, race*	5,634	0.97	0.92, 1.03
All person-level covariates†	5,634	0.98	0.92, 1.04
All person-level covariates and site‡	5,634	0.96	0.90, 1.02
All person-level covariates, site, copollutants, and weather§	5,047	0.92	0.85, 0.99
Prior 2 days			
Age, gender, race*	5,606	0.97	0.91, 1.04
All person-level covariates†	5,606	0.99	0.93, 1.06
All person-level covariates and site‡	5,606	0.97	0.90, 1.04
All person-level covariates, site, copollutants, and weather§	5,023	0.95	0.87, 1.04
Prior 7 days			
Age, gender, race*	5,510	1.01	0.93, 1.10
All person-level covariates†	5,510	1.05	0.96, 1.15
All person-level covariates and site‡	5,510	1.01	0.91, 1.12
All person-level covariates, site, copollutants, and weather§	4,913	1.00	0.88, 1.14
Prior 30 days			
Age, gender, race*	5,294	1.04	0.91, 1.18
All person-level covariates†	5,294	1.12	0.98, 1.29
All person-level covariates and site‡	5,294	1.09	0.92, 1.29
All person-level covariates, site, copollutants, and weather§	4,579	1.13	0.92, 1.40
Prior 60 days			
Age, gender, race*	5,136	1.01	0.87, 1.17
All person-level covariates†	5,136	1.12	0.96, 1.32
All person-level covariates and site‡	5,136	1.05	0.85, 1.31
All person-level covariates, site, copollutants, and weather§	4,219	1.03	0.79, 1.34

* Model variables: age (1 df), gender (1 df), and race/ethnicity (3 df).

† Model variables: age (1 df), gender (1 df), race/ethnicity (3 df), general health status (4 df), body mass index (1 df), diabetes (2 df), cigarette status (2 df), secondhand smoke (1 df), physical activity (2 df), arthritis flare in last 2 weeks (1 df), medications (aspirin, lipids, nonsteroidal anti-inflammatory drugs) (1 df), and infections in last 2 weeks (1 df).

‡ Model variables: age (1 df), gender (1 df), race/ethnicity (3 df), general health status (4 df), body mass index (1 df), diabetes (2 df), cigarette status (2 df), secondhand smoke (1 df), physical activity (2 df), arthritis flare in last 2 weeks (1 df), medications (aspirin, lipids, nonsteroidal anti-inflammatory drugs) (1 df), infections in last 2 weeks (1 df), and study site (5 df).

§ Model variables: age (1 df), gender (1 df), race/ethnicity (3 df), general health status (4 df), body mass index (1 df), diabetes (2 df), cigarette status (2 df), secondhand smoke (1 df), physical activity (2 df), arthritis flare in last 2 weeks (1 df), medications (aspirin, lipids, nonsteroidal anti-inflammatory drugs) (1 df), infections in last 2 weeks (1 df), study site (5 df), sulfur dioxide (1 df), nitrogen dioxide (1 df), carbon monoxide (1 df), ozone (1 df), average temperature (1 df), and dew point temperature (1 df).

Associations were of small magnitude and became even weaker after additional adjustment for site, copollutants, and weather, and confidence intervals of all estimates included the null value. Although stratified analyses suggested stronger associations in persons without other risk factors for elevated C-reactive protein, this heterogeneity

was not statistically significant. We also found no evidence of associations between particulate matter exposures and interleukin-6 (not shown).

Prior evidence regarding the relation between short-term exposures to particulate matter and C-reactive protein concentration is not entirely consistent. In one of the largest

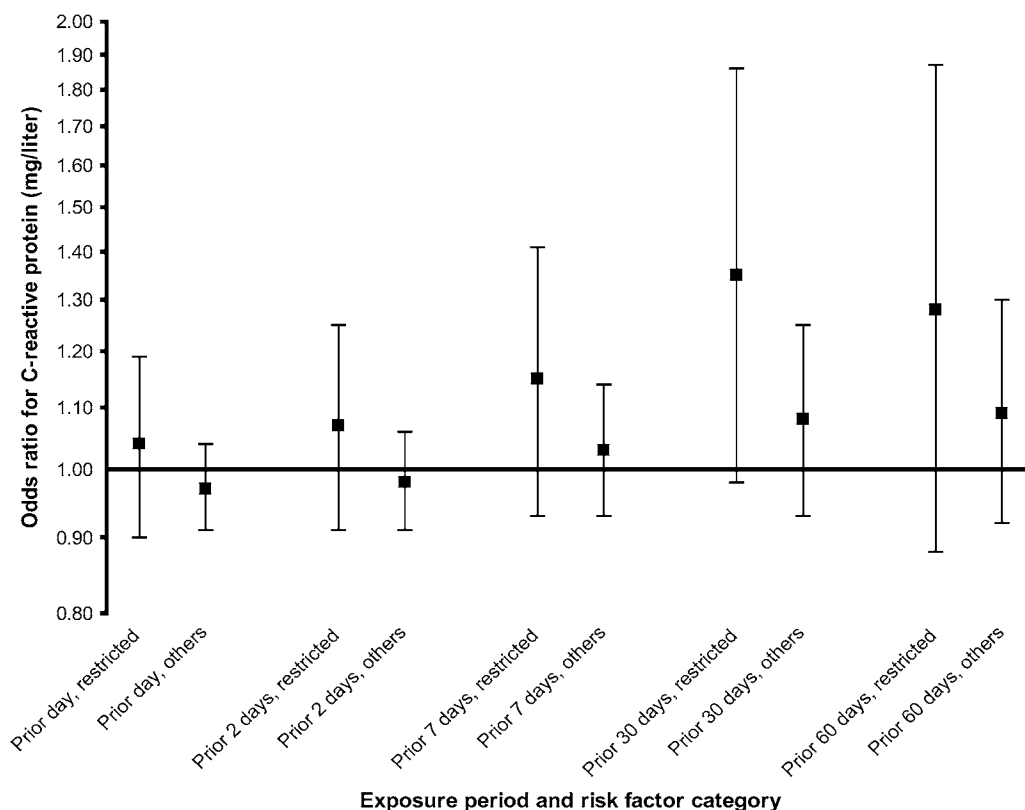


FIGURE 3. Odds ratios (with 95% confidence intervals) of C-reactive protein of ≥ 3 mg/liter per $10\text{-}\mu\text{g}/\text{m}^3$ increase in particulate matter of $\leq 2.5\text{ }\mu\text{m}$ in diameter for different exposure periods in a restricted sample without risk factors for elevated C-reactive protein and in the rest of the sample, adjusted for person-level covariates, Multi-Ethnic Study of Atherosclerosis, 2000–2002. The “restricted” sample (20%, $n = 1,123$) are nonsmokers without a history of recent infection or arthritis, in good to excellent health, with normal glucose, and who are not taking antiinflammatory medications; “others” are the participants not in the restricted sample. Analyses were adjusted for age, gender, race/ethnicity, general health status, body mass index, diabetes, cigarette smoking, secondhand smoke, physical activity, arthritis flare, medications, and infections. p values for interaction between exposure and sample group (restricted vs. other) were 0.5, 0.5, 0.5, 0.3, and 0.6 for the prior day, prior 2 days, prior 7 days, prior 30 days, and prior 60 days, respectively.

studies to date, Peters et al. (19) found that contemporaneous and recent (5 prior days) exposures to total suspended particulates were associated with C-reactive protein concentration in a sample of 631 men with two repeated measures. C-reactive protein increased 0.88 mg/liter for each $26\text{-}\mu\text{g}/\text{m}^3$ increase in the previous 5-day average level of total suspended particulates. Seaton et al. (22) found positive associations between recent (up to 3-day) city-level exposures to PM_{10} and C-reactive protein (147 percent increase in C-reactive protein per $100\text{-}\mu\text{g}/\text{m}^3$ increase in PM_{10}) in a sample of 112 persons with multiple repeated measures over 18 months, although no associations were observed for person-level measures of exposure. Pope et al. (23) found a positive association between recent (up to 3-day) $\text{PM}_{2.5}$ exposure and C-reactive protein in 88 subjects with a mean of 2.8 repeated measures, but this association disappeared when one influential subject was removed from the sample. One prior study has reported increases in interleukin-6 associated with PM_{10} exposure during an acute episode of air pollution in a sample of 30 healthy volunteers, but the magnitude of the increase in PM_{10} studied (from $40\text{ }\mu\text{g}/\text{m}^3$ to

$125\text{ }\mu\text{g}/\text{m}^3$) was much greater than the variation observed in our sample (10).

An advantage of our study over prior work is the large sample size, as well as the geographic and demographic diversity of the sample. Although there was limited within-site spatial variability in $\text{PM}_{2.5}$, at least as reflected by ambient monitors, our analyses rely more on day-to-day variability than on between-site or within-site variability. However, it is possible that the range of values present in our sample did not allow us to detect important threshold effects at the higher end of the particulate matter distribution. In a comparison of the magnitude of $\text{PM}_{2.5}$ exposure with US Environmental Protection Agency National Ambient Air Quality Standards, almost half (47 percent) of the sample had prior day $\text{PM}_{2.5}$ levels that exceeded the annual standard of $15\text{ }\mu\text{g}/\text{m}^3$, although less than 1 percent had prior day $\text{PM}_{2.5}$ levels that exceeded the 24-hour standard of $65\text{ }\mu\text{g}/\text{m}^3$. Two prior studies based on ambient monitoring that reported an association between exposure to particulate matter and C-reactive protein may have contrasted more extreme values by studying an air pollution episode (19)

or by purposely sampling high and low air pollution days (23), although at least one study has reported associations even at relatively low levels of PM_{2.5} exposures (34).

We relied on the existing ambient air-monitoring network to characterize exposures. Outdoor concentrations have been shown to be reasonable proxies for personal exposure to particles of outdoor origin (35, 36). Indoor exposures (such as those from passive smoking and wood-burning stoves and fireplaces) are important contributors to personal particle exposure and are not captured by the outdoor measurements. However, in order to be confounders of the effects we were interested in estimating, these indoor exposures would have to be associated with ambient levels on the day of the clinic examination, which is unlikely. Moreover, our results were adjusted for passive smoking, which is likely to be the major contributor to indoor exposures in the populations we studied.

The existing literature has characterized personal exposures based on monitor measurements averaged over very large areas: within a county (37), within a metropolitan area (38, 39), or within a city (40). Single "representative" monitors located in the center of a city have also been used (22, 41). We used data from the monitors closest to each participant's residence. Thirty-eight percent of study participants were not employed at the time of the survey (retired and not working, unemployed, or homemakers). In addition, over 75 percent of our participants reported spending 60 percent of their time either in their home or within 1 mile (1.6 km) of their home. This suggests that assignment of exposure based on place of residence is reasonable. We tested the sensitivity of our results to alternate ways of estimating exposure and found similar results when analyses were restricted to participants with monitors within 9 km of their home and when the exposure measure was based on the average of all available measurements within the study area. The high within-site correlation of monitor PM_{2.5} measures suggests that the results are unlikely to be highly sensitive to alternate methods, such as averaging over the specific areas within which participants are likely to move in the course of a usual day. The results were also robust to alternative interpolation methods.

There is little a priori knowledge on which to base hypotheses regarding the relevant lags expected between exposure to particulate matter and effects on inflammatory markers. Circulating C-reactive protein has a plasma half-life of only 19 hours and can be upregulated rapidly, within hours, during an acute-phase response (42). Human and animal experimental studies have found that an inflammatory response occurs 6–36 hours after exposure to particles (13–16). This evidence suggests that short-term lags are likely to be especially relevant for C-reactive protein. Pope et al. (23) found that concurrently measured PM_{2.5} was more strongly associated with C-reactive protein than were measures lagged 1 or 2 days, although an effect almost comparable with the concurrent day was observed for the average of the 3 days prior. Peters et al. (19) found that levels of C-reactive protein were positively associated with levels of total suspended particulates on the day of the examination. However, similar or slightly stronger associations were observed for total suspended particulates measured on the

prior day and for the mean of the prior 5 days, suggesting longer-term cumulative effects. In our analyses, the only weakly positive (albeit not statistically significant) associations were observed for the longer lags. Zanobetti et al. (43) recently reported a positive association between prior 60-day PM_{2.5} exposure and C-reactive protein concentration in a large population sample: C-reactive protein increased 7.7 percent per 10- $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} (95 percent CI: 0.96, 14.96). Given the relatively short half-life of C-reactive protein, it is difficult to reconcile the presence of long-term exposure effects with the absence of effects for shorter lags. An alternative explanation for associations with longer-term exposure periods is that the averaging process reduces measurement error and hence increases the ability to detect associations.

Similarly to some prior studies of air pollution exposures and inflammatory markers (20, 21, 41), our analyses are based on a single measure of C-reactive protein on each person. Therefore, inferences are based on between-person as opposed to within-person comparisons. This raises the possibility that associations (or the lack thereof) could result from confounding by individual-level characteristics. Our analyses controlled for a large set of variables associated with C-reactive protein levels. Analyses of residuals revealed no evidence of seasonal patterns or residual autocorrelation in adjusted models. It is therefore unlikely that our null findings are the result of individual-level confounding. Studies of repeated measures, however, which allow inferences to be drawn by within-person comparisons, do have greater power for detecting associations with exposures that change over time while holding time-independent individual-level factors constant (44). Repeated-measures analyses based on the MESA cohort will be possible as additional follow-up becomes available.

Measurement error in our exposure estimates may have biased results toward the null. More detailed assessment of personal exposures (involving activity diaries and additional monitoring both indoors and outdoors) currently planned for the MESA cohort will allow much more precise measurement of personal exposures. It is also plausible that improved measurement of specific components of PM_{2.5} (such as ultrafine particles or transition metals) may enhance our ability to detect effects on systemic inflammation (9). In any case, our results make it unlikely that a systemic inflammatory response explains the short-term effects of recent exposures observed in time-series analyses, which also rely exclusively on monitor data. Inconsistent results regarding the relation between ambient particulate matter mass and markers of systemic inflammation, plus persistent questions on the extent to which inflammation is a risk factor, risk marker, or simply a correlate of atherosclerosis (45), suggest that other mechanistic pathways linking particulate matter exposures to cardiovascular events need to be explored.

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REFERENCES

- Morris RD. Airborne particulates and hospital admissions for cardiovascular disease: a quantitative review of the evidence. *Environ Health Perspect* 2001;109(suppl 4):495–500.
- Samet JM, Dominici F, Currier FC, et al. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. *N Engl J Med* 2000;343:1742–9.
- Dockery DW. Epidemiologic evidence of cardiovascular effects of particulate air pollution. *Environ Health Perspect* 2001;109(suppl 4):483–6.
- Dockery DW, Pope CA 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 1993;329:1753–9.
- Pope CA 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002;287:1132–41.
- Pope CA 3rd, Thun MJ, Namboodiri MM, et al. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med* 1995;151:669–74.
- Seaton A, MacNee W, Donaldson K, et al. Particulate air pollution and acute health effects. *Lancet* 1995;345:176–8.
- Frampton MW. Systemic and cardiovascular effects of airway injury and inflammation: ultrafine particle exposure in humans. *Environ Health Perspect* 2001;109(suppl 4):529–32.
- Donaldson K, Stone V, Seaton A, et al. Ambient particle inhalation and the cardiovascular system: potential mechanisms. *Environ Health Perspect* 2001;109(suppl 4):523–7.
- van Eeden SF, Tan WC, Suwa T, et al. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM₁₀). *Am J Respir Crit Care Med* 2001;164:826–30.
- Ridker PM, Morrow DA. C-reactive protein, inflammation, and coronary risk. *Cardiol Clin* 2003;21:315–25.
- Nemmar A, Hoylaerts MF, Hoet PH, et al. Possible mechanisms of the cardiovascular effects of inhaled particles: systemic translocation and prothrombotic effects. *Toxicol Lett* 2004;149:243–53.
- Gardner SY, Lehmann JR, Costa DL. Oil fly ash-induced elevation of plasma fibrinogen levels in rats. *Toxicol Sci* 2000;56:175–80.
- Salvi S, Blomberg A, Rudell B, et al. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999;159:702–9.
- Salvi SS, Nordenhall C, Blomberg A, et al. Acute exposure to diesel exhaust increases IL-8 and GRO- α production in healthy human airways. *Am J Respir Crit Care Med* 2000;161:550–7.
- Ghio AJ, Kim C, Devlin RB. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. *Am J Respir Crit Care Med* 2000;162:981–8.
- Clarke RW, Catalano PJ, Koutrakis P, et al. Urban air particulate inhalation alters pulmonary function and induces pulmonary inflammation in a rodent model of chronic bronchitis. *Inhal Toxicol* 1999;11:637–56.
- Clarke RW, Coull B, Reinisch U, et al. Inhaled concentrated ambient particles are associated with hematologic and bronchoalveolar lavage changes in canines. *Environ Health Perspect* 2000;108:1179–87.
- Peters A, Frohlich M, Doring A, et al. Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg Study. *Eur Heart J* 2001;22:1198–204.
- Schwartz J. Air pollution and blood markers of cardiovascular risk. *Environ Health Perspect* 2001;109(suppl 3):405–9.
- Pekkanen J, Brunner EJ, Anderson HR, et al. Daily concentrations of air pollution and plasma fibrinogen in London. *Occup Environ Med* 2000;57:818–22.
- Seaton A, Soutar A, Crawford V, et al. Particulate air pollution and the blood. *Thorax* 1999;54:1027–32.
- Pope CA 3rd, Hansen ML, Long RW, et al. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. *Environ Health Perspect* 2004;112:339–45.
- Zanobetti A, Schwartz J, Samoli E, et al. The temporal pattern of mortality responses to air pollution: a multicity assessment of mortality displacement. *Epidemiology* 2002;13:87–93.
- Zanobetti A, Schwartz J, Samoli E, et al. The temporal pattern of respiratory and heart disease mortality in response to air pollution. *Environ Health Perspect* 2003;111:1188–93.
- Dominici F, McDermott A, Zeger SL, et al. Airborne particulate matter and mortality: timescale effects in four US cities. *Am J Epidemiol* 2003;157:1055–65.
- Goodman PG, Dockery DW, Clancy L. Cause-specific mortality and the extended effects of particulate pollution and temperature exposure. *Environ Health Perspect* 2004;112:179–85.
- Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871–81.
- Office of Air Quality Planning and Standards. AIRS (Aerometric Information Retrieval System). (Database). Research Triangle Park, NC: US Environmental Protection Agency, 2003. (<http://www.epa.gov/ttn/airs/airsaqs/>).
- Hastie T, Tibshirani R. Generalized additive models for medical research. *Stat Methods Med Res* 1995;4:187–96.
- Haas TC. Local prediction of a spatio-temporal process with an application to wet sulfate deposition. *J Am Stat Assoc* 1995;90:1189–99.
- Kyriakidis PC, Journel AG. Stochastic modeling of atmospheric pollution: a spatial time-series framework. Part II: application to monitoring monthly sulfate deposition over Europe. *Atmos Environ* 2001;35:2339–48.
- Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003;107:363–9.
- Riediker M, Cascio WE, Griggs TR, et al. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. *Am J Respir Crit Care Med* 2004;169:934–40.
- Janssen NA, Hoek G, Brunekreef B, et al. Personal sampling of particles in adults: relation among personal, indoor, and outdoor air concentrations. *Am J Epidemiol* 1998;147:537–47.
- Dockery DW, Spengler JD. Indoor-outdoor relationships of respirable sulfates and particles. *Atmos Environ* 1981;15:335–43.
- Liao D, Duan Y, Whitsel EA, et al. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. *Am J Epidemiol* 2004;159:768–77.

38. Samet JM, Dominici F, Zeger SL, et al. The National Morbidity, Mortality, and Air Pollution Study. Part I: methods and methodologic issues. *Res Rep Health Eff Inst* 2000;(94 pt 1): 5–14; discussion 75–84.
39. Schwartz J. Short term fluctuations in air pollution and hospital admissions of the elderly for respiratory disease. *Thorax* 1995;50:531–8.
40. Schwartz J. The distributed lag between air pollution and daily deaths. *Epidemiology* 2000;11:320–6.
41. Peters A, Doring A, Wichmann HE, et al. Increased plasma viscosity during an air pollution episode: a link to mortality? *Lancet* 1997;349:1582–7.
42. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;340:448–54.
43. Zanobetti A, Schwartz J, Ridker PM. Air pollution and markers of cardiovascular risk. (Abstract). *Epidemiology* 2004;15(suppl):S22.
44. Diggle PJ, Liang KY, Zeger SL. Design considerations. *Analysis of longitudinal data*. New York, NY: Oxford University Press, 2002:22–32.
45. Pearson RL, Wachtel H, Ebi KL. Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers. *J Air Waste Manag Assoc* 2000;50: 175–80.